FORM PTO-1390 (Modified) (REV 1-98) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: **PU3375USW**

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR): **09/529050**

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP98/06278	**5 October 1998**	**7 October 1997**

TITLE OF INVENTION
MEDICAMENTS

APPLICANT(S) FOR DO/EO/US
Allen Wayne MANGEL and Allison Ruth NORTHCUTT

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ A copy of the International Search Report (PCT/ISA/210).
8. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
9. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
10. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 13 to 20 below concern document(s) or information included:

13. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☒ Certificate of Mailing by Express Mail
20. ☒ Other items or information:

PCT REQUEST

Express Mail Label No.:
EL395890427US

422 Rec'd PCT/PTO 05 APR 2000

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
09/529050	PCT/EP98/06278	PU3375USW

21. The following fees are submitted:.

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :

		CALCULATIONS PTO USE ONLY
☐	Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2) paid to USPTO and International Search Report not prepared by the EPO or JPO **$970.00**	
☒	International preliminary examination fee (37 CFR 1.482) not paid to USPTO but Internation Search Report prepared by the EPO or JPO **$840.00**	
☐	International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$690.00**	
☐	International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$670.00**	
☐	International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) **$96.00**	
	ENTER APPROPRIATE BASIC FEE AMOUNT =	**$840.00**
	Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).	**$0.00**

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	12 - 20 =	0	x $18.00	**$0.00**
Independent claims	3 - 3 =	0	x $78.00	**$0.00**
Multiple Dependent Claims **(check if applicable)**.			☐	**$0.00**

TOTAL OF ABOVE CALCULATIONS =		**$840.00**
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28) **(check if applicable)**.	☐	**$0.00**
SUBTOTAL =		**$840.00**
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)).	+	**$0.00**
TOTAL NATIONAL FEE =		**$840.00**
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).**	☐	**$0.00**
TOTAL FEES ENCLOSED =		**$840.00**
	Amount to be: refunded	$
	charged	$

☐ A check in the amount of to cover the above fees is enclosed.

☒ Please charge my Deposit Account No. **07-1392** in the amount of **$840.00** to cover the above fees.
A duplicate copy of this sheet is enclosed.

☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. **07-1392** A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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SIGNATURE

Lorie Ann Morgan
NAME

38,181
REGISTRATION NUMBER

5 April ,2000
DATE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application:	A. Mangel et al.,		
Serial No.:	To be Assigned	Examiner:	To be Assigned
Filing Date:	Concurrently Herewith	Art Unit:	To be Assigned
For:	MEDICAMENTS		

Assistant Commissioner for Patents and Trademarks
Washington D.C. 20231

PRELIMINARY AMENDMENT

Sir:

Please amend and consider the instant application in view of the following amendments and remarks.

Amendment

In the Specification:

At page 1, line 1, please insert:

--This application is a Rule 371 Application of PCT/EP98/06278, filed 5 October 1998, which claims priority to Great Britain Patent Application No. 9721139.5, filed 7 October 1997.--

In the Claims:

Please cancel claims 1-4 and 9-10.

Please add the following new claims.

11. (New) A method of treatment of diarrhea-predominant female IBS which comprises administering an effective amount of a 5-HT_3 receptor antagonist or a pharmaceutically acceptable derivative thereof.

12. (New) A method of treatment according to claim 11, wherein the 5-HT_3 receptor antagonist is alosetron or a pharmaceutically acceptable derivative thereof.

13. (New) A method of treatment according to claim 12, wherein alosetron is in the form of its hydrochloride.

14. (New) A method of treatment according to claim 11, wherein the 5-HT3 receptor antagonist is selected from granisetron, azasetron, tropisetron, ramosetron, ondansetron, lerisetron, (R) zacopride, cliansetron, itasetron, indisetron or dolasetron.

15. (New) A method of treatment of alternating constipation/diarrhea IBS which comprises administering an effective amount of a 5-HT_3 receptor antagonist or a pharmaceutically acceptable derivative thereof.

16. (New) A method of treatment according to claim 15, wherein the 5-HT_3 receptor antagonist is alosetron or a pharmaceutically acceptable derivative thereof.

17. (New) A method of treatment according to claim 16, wherein alosetron is in the form of its hydrochloride.

18. (New) A method of treatment according to claim 15, wherein the 5-HT3 receptor antagonist is selected from granisetron, azasetron, tropisetron, ramosetron, ondansetron, lerisetron, (R) zacopride, cliansetron, itasetron, indisetron or dolasetron.

Remarks

Currently Claims 5-8, and 11-18 are pending. Claims 1-4 and 9-10 have been canceled to comply with standard U.S. practice.

An abstract on a separate page is provided herewith.

New claims 11-18 have been added to complete the record. Support for these claims can be found in Applicants' original specification (including the claims), and particularly at page 3 of Applicants' original specification.

Applicants respectfully submit that the instant application is in condition for substantive examination, which action is respectfully requested. The Examiner is invited to contact the undersigned at 483-8222, to discuss this case further if desired.

Respectfully submitted,

Lorie Ann Morgan

Attorney for Applicants
Registration No. 38,181

Date: 5 April, 2000
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I hereby certify that this correspondence is being deposited with the United States Postal Service as express mail in an envelope addressed to: Assistant Commissioner for Patents, USPTO Washington, DC 20231 on April 5, 2000 in accordance with the provisions of37 CFR § 1.8.

Keysha Bishop
Keysha Bishop

lam/i:/gi/alos/pu3375/pre-amend.doc

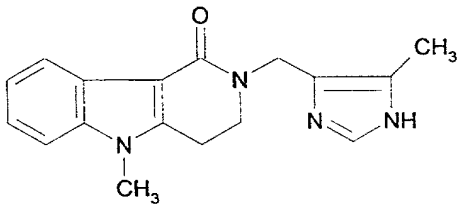
MEDICAMENTS

The invention relates to a new medical use for compounds which act as antagonists of 5-hydroxytryptamine (5-HT) at 5-HT_3 receptors.

5-HT_3 receptor antagonists may be identified by methods well known in the art, for example by their ability to inhibit 3-(5-methyl-1H-imidazole-4-yl)-1-[1-[^{3}H]-methyl-1H-indol-3-yl]-1-propanone binding in rat entorhinal cortex homogenates (following the general procedure described by G Kilpatrick *et al*, Nature, 1987, 330, 746-748), and/or by their effect on the 5-HT-induced Bezold-Jarisch (B-J) reflex in the cat (following the general method described by A Butler *et al*, Br. J. Pharmacol., 94, 397-412 (1988)).

A number of different 5-HT_3 receptor antagonists have been disclosed, for example those of group A: indisetron, Ro-93777, YM-114, granisetron, talipexole, azasetron, tropisetron, mirtazapine, ramosetron, ondansetron, lerisetron, alosetron, N-3389, zacopride, cilansetron, E-3620, lintopride, KAE-393, itasetron, mosapride and dolasetron.

In UK Patent No. 2209335, incorporated herein by reference, there is disclosed, *inter alia,* the compound 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one, now known as alosetron, which may be represented by the formula (I):



(I)

and pharmaceutically acceptable salts, solvates and pharmaceutically acceptable equivalents thereof, in particular its hydrochloride salt.

5-HT_3 receptor antagonists are known to be useful in the treatment of a variety of conditions involving 5-HT_3 receptor-mediated mechanisms, including in particular emesis.

Irritable bowel syndrome (IBS) is the most common diagnosis made by gastroenterologists (1) and is characterised by abdominal pain and discomfort and altered bowel functions (2-4). To date, no laboratory or structural defects have been identified in IBS and the formal diagnosis is based upon a constellation of symptoms defined by either the Manning (5) or Rome Criteria (6).

The current understanding of the pathophysiology or aetiology of IBS is limited, and no proven effective therapy is available (3,7). Moreover, many patients gain slight or even no relief from such therapies. Thus, there is a real need to develop new medicines for the treatment of IBS.

Over the last two decades compelling evidence has accumulated that a state of enhanced perception of visceral stimuli develops in patients with IBS (2,3,8-10). In balloon distension studies of the colon or rectum the threshold for sensation of pain is lower in IBS patients compared to controls, and this has been proposed as a biological marker for IBS (11). In view of the evidence for enhanced visceral perception in IBS and the frequent occurrence of pain, any agent considered to be of utility in the treatment of IBS should demonstrate effectiveness in the relief of pain.

Of the classes of therapeutic agents which have been proposed for the treatment of abdominal pain in IBS, 5-HT_3 receptor antagonists are among the most promising. In animal models, these agents have been shown to decrease visceral pain responses (12,13). Furthermore, the 5-HT_3 receptor antagonist, ondansetron, has been shown to slow colonic transit in normal volunteers (14-15). In patients with IBS ondansetron increases rectal compliance (16) and in diarrhoea-predominant IBS patients ondansetron improves stool consistency (17-19). Ondansetron also inhibits the contractile response of the colon in healthy volunteers in the early postprandial period (20), the time when many IBS patients experience symptoms. A second 5-HT_3 receptor antagonist, granisetron, has also been shown to produce a decrease in rectal sensitivity, and reduce post-prandial motor activity in IBS patients (21).

Alosetron is a potent and selective 5-HT_3 receptor antagonist, and in preliminary reports, alosetron has been shown to improve abdominal pain (22), and to slow colonic transit in IBS patients (23).

Surprisingly, it has now been found that 5-HT_3 receptor antagonists represent a particularly effective and well tolerated therapy in nonconstipated female IBS patients.

According to one aspect the invention therefore provides a 5-HT_3 receptor antagonist or a pharmaceutically acceptable derivative thereof for use in the treatment of nonconstipated female IBS.

In one preferred aspect the invention provides a 5-HT_3 receptor antagonist or a pharmaceutically acceptable derivative thereof for use in the treatment of diarrhoea predominant female IBS.

In another preferred aspect the invention provides a 5-HT_3 receptor antagonist or a pharmaceutically acceptable derivative thereof for use in the treatment of alternating constipation/diarrhoea IBS.

By pharmaceutically acceptable derivative is meant any pharmaceutically acceptable salt or solvate of a 5-HT_3 receptor antagonist or any other compound, which upon administration to the recipient is capable of providing (directly or indirectly) a 5-HT_3 receptor antagonist or an active metabolite or residue thereof.

In one preferred aspect the invention provides a compound of Group A or a pharmaceutically acceptable derivative thereof for use in the treatment of nonconstipated female IBS.

In a further preferred aspect the invention therefore provides alosetron or a pharmaceutically acceptable derivative thereof for use in the treatment of nonconstipated female IBS.

Suitable pharmaceutically acceptable salts of alosetron include acid addition salts formed with inorganic or organic acids (for example hydrochlorides, hydrobromides, sulphates, phosphates, benzoates, naphthoates,

hydroxynaphthoates, p-toluenesulphonates, methanesulphonates, sulphamates, ascorbates, tartrates, salicylates, succinates, lactates, glutarates, glutaconates, acetates, tricarballylates, citrates, fumarates and maleates), and solvates (for example hydrates) thereof.

In a preferred embodiment of the present invention alosetron is employed in the form of its hydrochloride.

In another aspect, the invention provides the use of a 5-HT_3 receptor antagonist or a pharmaceutically acceptable derivative thereof in the manufacture of a medicament for the treatment of nonconstipated female IBS.

In another aspect, the invention provides a method of treatment of nonconstipated female IBS which comprises administering an effective amount of a 5-HT_3 receptor antagonist or a pharmaceutically acceptable derivative thereof.

Within the above aspects and preferred aspects of the invention, the use of a 5-HT_3 receptor antagonist of Group A, more preferably alosetron, is especially preferred.

It is to be understood that reference to treatment includes both treatment of established symptoms and prophylactic treatment, unless explicitly stated otherwise.

Conveniently, a 5-HT_3 receptor antagonist or a pharmaceutically acceptable derivative thereof may be formulated in conventional manner using one or more pharmaceutically acceptable carriers or excipients. Thus a 5-HT_3 receptor antagonist or a pharmaceutically acceptable derivative thereof may, for example, be formulated for oral, sub-lingual, buccal, parenteral, rectal or intranasal administration, or in a form suitable for administration by inhalation or insufflation (either through the mouth or nose), or in a form suitable for topical administration.

For oral administration the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g.

pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrates (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters or ethyl alcohol); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid).

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

For parenteral administration the compositions may take the form of injections, conveniently intravenous, intramuscular or subcutaneous injections, for example bolus injections or continuous intravenous infusions. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, optionally with an added preservative.

The compositions for parenteral administration may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the compositions may be in dry form such as a powder, crystalline or freeze-dried solid for constitution with a suitable vehicle, e.g. sterile pyrogen-free water or isotonic saline before use. They may be presented, for example, in sterile ampoules or vials.

For rectal administration the compositions may take the form of suppositories or retention enemas.

Tablets for sub-lingual administration may be formulated in a conventional manner.

For intranasal administration, or administration by inhalation or insufflation, conventional formulations may be employed.

For topical administration the pharmaceutical compositions may be liquids, for example solutions, suspensions or emulsions presented in the form of creams or gels.

In addition to the formulations described previously, the compositions may also be formulated as a depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously, transcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compositions may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

It will be appreciated that the precise therapeutic dose of a 5-HT_3 receptor antagonist, expressed in the form of its free base, will depend on the age and condition of the patient and the nature of the IBS to be treated, and will be at the ultimate discretion of the attendant physician.

However, in general, effective doses for the treatment of nonconstipated female IBS patients will lie in the range of 0.001 to 500mg, such as 0.01 to 100mg, preferably 0.05 to 50mg, for example 0.5 to 25mg per unit dose, which could be administered in single or divided doses, for example, 1 to 4 times per day.

In a preferred embodiment, effective doses of alosetron for the treatment of nonconstipated female IBS patients will lie in the range of 0.01 to 100mg, such as 0.05 to 50mg, preferably 0.1 to 25mg, for example 0.5, 1, 2 or 4mg of alosetron per unit dose, which could be administered in single or divided doses, for example, 1 to 4 times per day.

The use of alosetron in the treatment of nonconstipated female IBS patients is supported by the following clinical data.

Patients

Three hundred and seventy IBS patients were randomised for study: 80 were randomised to treatment with placebo BID, 72 to 1 mg BID alosetron, 74 to 2 mg BID alosetron, 76 to 4 mg BID alosetron and 68 to 8 mg BID alosetron. Table 1 shows the demographic characteristics for patients in all 5 treatment groups, and characteristics were similar between treatment arms. Patients were required to have symptoms which fulfilled the Rome Criteria for IBS (5) for at least 6 months. Because of the ability of 5-HT_3 -receptor antagonists to slow colonic transit (14-15), constipation-predominant IBS patients were excluded from this study, and only patients with diarrhoea-predominant IBS or alternating constipation/diarrhoea were included.

Study Design

Daily and weekly symptom data were collected using a recently described electronic touch-tone telephone based system (24,25). Patients underwent a 2 week screening period with no IBS treatment to ensure sufficient baseline level of abdominal pain as well as compliance with the data collection system. Pain was assessed daily on a 5 point scale (0=none; 1=mild; 2=moderate; 3=intense; 4=severe). Average baseline pain over the 2 week screening period was required to be between 1.5-3.3, inclusive, and at least 4 days with at least moderate pain was required for enrolment into the study. Stool consistency data were also collected (1=very hard; 2=hard; 3=formed; 4=loose; and 5=watery). During the screening period an average stool consistency score of $\geq$2.5 was required for entry into the study in order to exclude those with predominant constipation.

Following the screening period, eligible patients were randomised with equal allocation to 12 weeks of study medication (BID) of placebo or alosetron 1, 2, 4 or 8 mg taken prior to meals. Patients were followed for 2 weeks post-treatment. During the screening period, treatment phase and follow-up period, patients were asked daily questions about their IBS symptoms. Once every 7 days, during the treatment phase of the study, patients responded to an additional question as to whether they had obtained adequate relief of their IBS- related abdominal pain and discomfort during the previous 7 days.

Statistics

For this study, a responder was prospectively defined as a patient who completed the treatment phase of the study and reported adequate relief of their IBS pain and discomfort for at least 6 weeks. Responders for adequate relief have been shown to display a strong correlation with improvement in abdominal pain, bowel function and quality of life as compared to nonresponders (26). In addition, a monthly responder was defined as a patient who reported adequate relief of their IBS pain and discomfort for at least 2 weeks per month. For the monthly analysis, a last observation carried forward procedure was employed, whereby a month with all missing weeks was assigned the number of weeks with adequate relief from the previous non-missing month. Thus, this analysis satisfied the Intent-to-Treat principle by including all patients and months. Treatment groups were compared for the proportion of patients defined as responders, for both endpoints, using a Mantel-Haenszel test stratified for investigator cluster. Finally, the proportion of weeks with adequate relief was compared between treatment groups using a log-rank test.

Daily stool consistency scores and daily number of bowel movements were averaged over the baseline, weekly for weeks 1-4, and monthly (weeks 1-4, 5-8, and 9-12) intervals. In addition, the proportion of days patients experienced a sense of urgency was calculated over the monthly and weekly intervals. For the monthly intervals, the treatment groups were compared for change from baseline using a van Elteren test adjusted for investigator cluster. For the weekly intervals, the treatment groups were compared at each week using a van Elteren test adjusted for investigator cluster.

Adequate Relief of Pain and Discomfort

% Responders	Alosetron (mg BID)				
	Placebo	1	2	4	8
FEMALE	33	60	59	51	52
MALE	53	20	50	54	52

Examination of each dose of alosetron showed a greater proportion of female responders for adequate relief as compared with placebo. The largest treatment effect occurred with 1 mg BID alosetron where 27% more responders were observed as compared to that seen with placebo (33% placebo vs 60% alosetron; p=0.013). A similar result was observed with 2 mg BID alosetron where 59% responders were seen (p=0.026). No meaningful improvement relative to placebo was seen in the male population with any dose of alosetron. However, the placebo response in males was substantially greater than that seen in females.

% Weeks with adequate relief	Alosetron (mg BID)				
	Placebo	1	2	4	8
FEMALE	33	58	50	50	50

The proportion of weeks with adequate relief was also evaluated. Placebo treated female patients had a median 33% of weeks with adequate relief. With 1 mg BID alosetron, female patients reported adequate relief for a median 58% of the weeks (p=0.039). In the treatment groups receiving greater than 1 mg alosetron (i.e., 2 mg, 4 mg and 8 mg BID) female patients reported having adequate relief for a median 50% of the weeks with each of the doses of alosetron. By contrast, male patients received no meaningful benefit with respect to the proportion of weeks with adequate relief with alosetron.

% Responders	Monthly Intervals		
	1	2	3
Placebo	32	42	36
Alosetron 1mg BID	53	62	60

In order to identify how rapidly alosetron produces adequate relief, we analysed adequate relief during each of the three months of the study. With 1 mg BID alosetron, statistically significant improvement occurred for female patients during each month. Increases of 21%, 20% and 24% above placebo were seen at months 1,2 and 3, respectively. Alosetron 1 mg was superior to the other alosetron (2,4, or 8 mg) evaluated. No improvement relative to placebo was seen among males at any month, with any dose of alosetron.

Improvement in Bowel Habits

In females patients, most doses of alosetron significantly improved stool consistency, bowel movement frequency and the proportion of days with urgency as compared to placebo (Table 2). For each of these parameters, a statistically significant benefit over placebo was achieved after 1 week of treatment and benefit persisted throughout the remainder of the 12 week treatment period. Among males, no significant improvement over placebo was seen in the bowel-related functions with the exception of stool consistency. Stool consistency in males improved significantly with doses of alosetron higher than 1 mg BID.

These results demonstrate that alosetron significantly improved abdominal pain and bowel function in female IBS patients. Alosetron also significantly improved, in female patients, three clinically relevant bowel related functions: number of bowel movements per day, stool consistency, and sense of urgency. All of these parameters were significantly improved within the first week of treatment and were sustained throughout the three month study.

Surprisingly, alosetron-mediated improvement in the efficacy parameters, with the exception of hardening in stool consistency, were found to occur only in females.

Based upon the results of the present study, alosetron appears to represent an effective and well tolerated therapy in nonconstipated female IBS patients.

Table 1

Demographic Characteristics

		Alosetron BID			
Characteristic n	Placebo 80	1mg 72	2mg 74	4mg 76	8mg 68
Age (yrs)	43.3 ± 14.9	44.7 ± 13.5	43.9 ± 14.9	44.3 ± 11.9	45.1 ± 14.8
Sex					
Male	21 (26%)	19 (26%)	23 (31%)	21 (28%)	28 (41%)
Female	59 (74%)	53 (74%)	51 (69%)	55 (72%)	40 (59%)
Race					
Caucasian	76 (95%)	67 (93%)	67 (91%)	75 (99%)	63 (93%)
Black	3 (4%)	3 (4%)	4 (5%)	0 (0%)	0 (0%)
Other	1 (1%)	2 (3%)	3 (4%)	1 (1%)	5 (6%)
Females					
Post-Menopausal	10 (17%)	9 (17%)	9 (18%)	9 (16%)	8 (20%)
Sterile	25 (42%)	29 (55%)	25 (49%)	35 (64%)	19 (48%)
Child-bearing Potential	24 (41%)	15 (28%)	17 (33%)	11 (20%)	13 (33%)
Duration of IBS Symptoms (yrs)	9.8 ± 10.9	10.3 ± 10.4	9.4 ± 9.9	9.9 ± 9.3	9.3 ± 7.7
Baseline Pain	2.23 ± 0.47	2.12 ± 0.48	2.11 ± 0.42	2.22 ± 0.48	2.30 ± 0.47

Pain score: 0=none, 1=mild, 2=moderate, 3=intense, 4=severe

Table 1

Demographic Characteristics

		Alosetron BID			
Characteristic n	Placebo 80	1mg 72	2mg 74	4mg 76	8mg 68
Age (yrs)	43.3 ± 14.9	44.7 ± 13.5	43.9 ± 14.9	44.3 ± 11.9	45.1 ± 14.8
Sex					
Male	21 (26%)	19 (26%)	23 (31%)	21 (28%)	28 (41%)
Female	59 (74%)	53 (74%)	51 (69%)	55 (72%)	40 (59%)
Race					
Caucasian	76 (95%)	67 (93%)	67 (91%)	75 (99%)	63 (93%)
Black	3 (4%)	3 (4%)	4 (5%)	0 (0%)	0 (0%)
Other	1 (1%)	2 (3%)	3 (4%)	1 (1%)	5 (6%)
Females					
Post-Menopausal	10 (17%)	9 (17%)	9 (18%)	9 (16%)	8 (20%)
Sterile	25 (42%)	29 (55%)	25 (49%)	35 (64%)	19 (48%)
Child-bearing Potential	24 (41%)	15 (28%)	17 (33%)	11 (20%)	13 (33%)
Duration of IBS Symptoms (yrs)	9.8 ± 10.9	10.3 ± 10.4	9.4 ± 9.9	9.9 ± 9.3	9.3 ± 7.7
Baseline Pain	2.23 ± 0.47	2.12 ± 0.48	2.11 ± 0.42	2.22 ± 0.48	2.30 ± 0.47

Pain score: 0=none, 1=mild, 2=moderate, 3=intense, 4=severe

Table 2

Effects of Alosetron on Bowel Function In Female Patients With IBS

		Alosetron BID			
Function	Placebo	1 mg	2 mg	4 mg	8 mg
(n)	(59)	(53)	(51)	(55)	(40)
% Days with Urgency	54.3± 32.04	33.0± 28.8*	35.9± 34.4**	37.8± 34.2*	41.5± 33.6
Stool # per day	2.2± 1.35	1.4± 1.0 *	1.7± 0.9 *	1.8± 1.2 *	1.3± 0.7 *
Stool Consistentcy	2.9± 0.69	2.1± 0.83**	2.2± 0.73**	2.4± 0.74**	1.8± 0.64**

mean ± SD

Data collected from week 9-12 interval

p-values are based on change from baseline

* $p \leq 0.01$ with respect to placebo

** $p \leq 0.001$ with respect to placebo

Consistency score: 1=very hard, 2=hard, 3=formed, 4=loose, 5=watery

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Claims

1. Use of a 5-HT_3 receptor antagonist or a pharmaceutically acceptable derivative thereof in the manufacture of a medicament for the treatment of nonconstipated female IBS.

2. Use according to claim 1 wherein the 5-HT_3 receptor antagonist is alosetron or a pharmaceutically acceptable derivative.

3. Use according to claim 2 wherein alosetron is in the form of its hydrochloride.

4. Use according to claim 1 wherein the 5-HT_3 receptor antagonist is selected from granisetron, azasetron, tropisetron, ramosetron, ondansetron, lerisetron, (R) zacopride, cilansetron, itasetron, indisetron or dolasetron.

5. A method of treatment of nonconstipated female IBS which comprises administering an effective amount of a 5-HT_3 receptor antagonist or a pharmaceutically acceptable derivative thereof.

6. A method of treatment according to claim 5 wherein the 5-HT_3 receptor antagonist is alosetron or a pharmaceutically acceptable derivative.

7. A method of treatment according to claim 6 wherein alosetron is in the form of its hydrochloride.

8. A method of treatment according to claim 5 wherein the 5-HT_3 receptor antagonist is selected from granisetron, azasetron, tropisetron, ramosetron, ondansetron, lerisetron, (R) zacopride, cilansetron, itasetron, indisetron or dolasetron.

9. A 5-HT_3 receptor antagonist or a pharmaceutically acceptable derivative thereof for use in the treatment of nonconstipated female IBS.

10. A 5-HT_3 receptor antagonist according to claim 9 which is alosetron, or alosetron in the form of its hydrochloride.

Abstract

This invention relates to the use of 5-HT3 receptor antagonists in the treatment of nonconstipated female IBS patients.

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY
(Includes Reference to PCT International Applications)

ATTORNEY'S DOCKET NUMBER
PU3375USW

As below named inventor. I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

MEDICAMENTS

the specification of which (check only one item below):

[ ]is attached hereto.

[ ]was filed as United States application Serial No. _____on _____and was amended on (if applicable)

[**X**] was filed as PCT international application Number PCT/EP98/06278 on 5 October 1998

and was amended under PCT Article 19 on _____(if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 and all information which became available between the filing of the prior application and the national or PCT international filing date of the continuation-in-part application.

I hereby claim foreign priority benefits under Title 35, United States Code. §119 (a)-(d) or §365(b) of any foreign applications(s) for patent or inventor's certificate or 365(a) of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) having a filing date before that of the application(s) on which priority is claimed:

PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:

COUNTRY (if PCT indicate PCT)	APPLICATION NUMBER		PRIORITY CLAIMED UNDER 35 USC 119
1. GB	9721139.5	7 October 1997	X
2. PCT	PCT/EP98/06278	5 October 1998	X
3.			
4.			
5.			

I hereby claim the benefit under Title 35, United States Code §119(e) of any United States provisional application(s) listed below:

Application No..	Filing Date (MM/DD/YYYY)	
1.		
2.		
3.		
4.		
5.		

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COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY (Continued - Includes References to PCT International Applications)

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I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) or §365(c) of any PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application(s) and the national or PCT international filing date of this application:

PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT UNDER 35 U.S.C. 120:

U.S. APPLICATIONS		STATUS (Check one)		
U.S. APPLICATION NUMBER	U.S. FILING DATE	PATENTED	PENDING	ABANDONED

PCT APPLICATIONS DESIGNATING THE U.S.					
PCT APPLICATION NO.	PCT FILING DATE	U.S.FILING NUMBERS ASSIGNED (if any)			
PCT/EP98/06278	5 October 1998			X	

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signature of Inventor 201	Signature of Inventor 202	Signature of Inventor 203
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